

## CLAIMS

1. A crystallization method of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
5 N-carboxylic anhydride  
which comprises mixing a solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride in a good solvent with an aliphatic  
hydrocarbon solvent to crystallize said N-carboxylic anhydride,  
10 the solution of said N-carboxylic anhydride in the good  
solvent being added to the aliphatic hydrocarbon solvent to  
thereby effect crystallization while inhibiting an oil formation  
and scaling of said N-carboxylic anhydride.
- 15 2. The crystallization method according to Claim 1  
wherein a temperature at addition of the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride in the good solvent to the aliphatic  
hydrocarbon solvent is not higher than 60°C.
- 20 3. The crystallization method according to Claim 2  
wherein the temperature at addition of the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride in the good solvent to the aliphatic  
25 hydrocarbon solvent is -30 to 50°C.
4. The crystallization method according to Claim 3  
wherein the temperature at addition of the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
30 N-carboxylic anhydride in the good solvent to the aliphatic  
hydrocarbon solvent is -20 to 45°C.
5. The crystallization method according to any one of  
Claims 1 to 4  
35 wherein the aliphatic hydrocarbon solvent is a saturated

hydrocarbon of 5 to 12 carbon atoms represented by  $C_nH_{2n+2}$  or  $C_nH_{2n}$ , an unsaturated hydrocarbon of 5 to 12 carbon atoms represented by  $C_nH_{2n}$  or  $C_nH_{2n-2}$  or a mixed solvent thereof.

5           6. The crystallization method according to Claim 5  
          wherein the aliphatic hydrocarbon solvent is a saturated  
hydrocarbon solvent of 5 to 12 carbon atoms represented by  $C_nH_{2n+2}$   
or  $C_nH_{2n}$  or a mixed solvent thereof.

10           7. The crystallization method according to Claim 6  
          wherein the aliphatic hydrocarbon solvent is pentane,  
2-methylpentane, normal hexane, isohexane, normal heptane,  
normal octane, cyclohexane, methylcyclohexane,  
ethylcyclohexane, propylcyclohexane or a mixed solvent thereof.

15           8. The crystallization method according to Claim 7  
          wherein the aliphatic hydrocarbon solvent is normal  
hexane, isohexane, normal heptane, methylcyclohexane or a mixed  
solvent thereof.

20           9. The crystallization method according to any one of  
Claims 1 to 8  
          wherein the good solvent is a hydrogenated hydrocarbon,  
an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

25           10. The crystallization method according to Claim 9  
          wherein the good solvent is dichloromethane,  
1,1-dichloroethane, 1,2-dichloroethane,  
1,1,1-trichloroethane, 1,1,2-trichloroethane,  
30   tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether,  
acetoneitrile, ethyl acetate, methyl acetate, propyl acetate,  
isopropyl acetate, butyl acetate, isobutyl acetate, pentyl  
acetate, methyl propionate, ethyl propionate, acetone, methyl  
ethyl ketone or a mixed solvent thereof.

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11. The crystallization method according to Claim 9 wherein the good solvent is a halogenated hydrocarbon, an ether, an ester or a mixed solvent thereof.

5 12. The crystallization method according to Claim 11 wherein the good solvent is dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, ethyl  
10 acetate, methyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, pentyl acetate, methyl propionate, ethyl propionate or a mixed solvent thereof.

13. The crystallization method according to Claim 11  
15 wherein the good solvent is a halogenated hydrocarbon.

14. The crystallization method according to Claim 13 wherein the good solvent is dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane,  
20 1,1,1-trichloroethane, 1,1,2-trichloroethane or a mixed solvent thereof.

15. The crystallization method according to Claim 14 wherein the good solvent is dichloromethane.  
25

16. The crystallization method according to any one of Claims 1 to 15 wherein the addition of the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
30 N-carboxylic anhydride in the good solvent is carried out by a sequential addition.

17. The crystallization method according to Claim 16 wherein the sequential addition of the solution of  
35 N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine

N-carboxylic anhydride in the good solvent is carried out over not less than 1/4 of an hour.

18. The crystallization method according to any one of  
5 Claims 1 to 17

wherein the addition of the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride in the good solvent to the aliphatic  
hydrocarbon solvent is carried out in a condition that a crystal  
10 of said N-carboxylic anhydride is added to said aliphatic  
hydrocarbon solvent in advance.

19. The crystallization method according to Claim 18  
wherein an amount of the crystal of  
15 N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride to be added in advance is not more than  
30 weight % based on the total amount of said N-carboxylic  
anhydride in the solution in the good solvent to be subsequently  
added.

20. The crystallization method according to any one of  
Claims 1 to 19

wherein the addition of the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
25 N-carboxylic anhydride in the good solvent to the aliphatic  
hydrocarbon solvent is carried out by adding a portion of said  
solution in the good solvent to said aliphatic hydrocarbon  
solvent in advance to thereby prepare a slurry in which said  
N-carboxylic anhydride is precipitated, followed by adding the  
30 rest of said solution in a good solvent to said slurry.

21. The crystallization method according to Claim 20  
wherein an amount of the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
35 N-carboxylic anhydride in the good solvent to be added in advance

is not more than 30 weight % based on the total amount of the solution in the good solvent to be added.

22. The crystallization method according to any one of  
5 Claims 1 to 21

wherein an amount of a precipitated crystal is increased by adjusting a liquid temperature to -30 to 25°C following completion of the addition.

23. The crystallization method according to any one of  
10 Claims 1 to 22

wherein a weight ratio of the good solvent to the aliphatic hydrocarbon solvent at completion of the addition is 0.001 to 1.

24. The crystallization method according to Claim 23  
15 wherein the weight ratio of the good solvent to the aliphatic hydrocarbon solvent at completion of the addition is 0.003 to 1.

25. The crystallization method according to any one of  
20 Claims 1 to 24

wherein the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
25 N-carboxylic anhydride in the good solvent is  
an NCA forming reaction solution obtained by reacting  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with  
N,N'-carbonyldiimidazole or phosgene or  
a solution obtained by subjecting the reaction solution  
30 to concentration or solvent exchange.

26. The crystallization method according to Claim 25  
wherein an impurity or a coloring component as the  
byproduct of the NCA forming reaction is removed by using an  
35 adsorbent prior to the crystallization.

27. The crystallization method according to Claim 25 or  
26

5 wherein an NCA forming reaction solvent doubles as the  
good solvent for the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride in the good solvent.

28. A crystallization method of  
10 N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride

which comprises adding an aliphatic hydrocarbon solvent  
to a solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-  
L-alanine N-carboxylic anhydride in a good solvent to crystallize  
15 said N-carboxylic anhydride,

the aliphatic hydrocarbon solvent being added  
sequentially over not less than 1/4 of an hour and at a temperature  
of not higher than 60°C to thereby inhibit an oil formation and  
scaling of said N-carboxylic anhydride.  
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29. The crystallization method according to Claim 28  
wherein a temperature at addition of the aliphatic  
hydrocarbon solvent to the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
25 N-carboxylic anhydride in the good solvent is -30 to 50°C.

30. The crystallization method according to Claim 29  
wherein the temperature at addition of the aliphatic  
hydrocarbon solvent to the solution of  
30 N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride in the good solvent is 0 to 45°C.

31. The crystallization method according to any one of  
Claims 28 to 30  
35 wherein the aliphatic hydrocarbon solvent is a saturated

hydrocarbon of 5 to 12 carbon atoms represented by  $C_nH_{2n+2}$  or  $C_nH_{2n}$ , an unsaturated hydrocarbon of 5 to 12 carbon atoms represented by  $C_nH_{2n}$  or  $C_nH_{2n-2}$ , or a mixed solvent thereof.

5           32. The crystallization method according to Claim 31 wherein the aliphatic hydrocarbon solvent is a saturated hydrocarbon of 5 to 12 carbon atoms represented by  $C_nH_{2n+2}$  or  $C_nH_{2n}$ , or a mixed solvent thereof.

10           33. The crystallization method according to Claim 32 wherein the aliphatic hydrocarbon solvent is pentane, 2-methylpentane, normal hexane, isohexane, normal heptane, normal octane, isooctane, normal decane, cyclopentane, cyclohexane, methylcyclohexane, ethylcyclohexane,  
15 propylcyclohexane or a mixed solvent thereof.

            34. The crystallization method according to Claim 33 wherein the aliphatic hydrocarbon solvent is normal hexane, isohexane, normal heptane, isooctane, methylcyclohexane or a  
20 mixed solvent thereof.

            35. The crystallization method according to any one of Claims 28 to 34 wherein the good solvent is a halogenated hydrocarbon,  
25 an ether, a nitrile, an ester, a ketone or a mixed solvent thereof.

            36. The crystallization method according to Claim 35 wherein the good solvent is a halogenated hydrocarbon, an ether, an ester or a mixed solvent thereof.  
30

            37. The crystallization method according to Claim 36 wherein the good solvent is a halogenated hydrocarbon.

            38. The crystallization method according to Claim 35 wherein the good solvent is dichloromethane,  
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1,1-dichloroethane, 1,2-dichloroethane,  
 1,1,1-trichloroethane, 1,1,2-trichloroethane,  
 tétrahydrofuran, 1,4-dioxane, t-butyl methyl ether,  
 acetonitrile, ethyl acetate, methyl acetate, propyl acetate,  
 5 isopropyl acetate, butyl acetate, isobutyl acetate, pentyl  
 acetate, methyl propionate, ethyl propionate, acetone, methyl  
 ethyl ketone or a mixed solvent thereof.

39. The crystallization method according to Claim 36  
 10 wherein the good solvent is dichloromethane,  
 1,1-dichloroethane, 1,2-dichloroethane,  
 1,1,1-trichloroethane, 1,1,2-trichloroethane,  
 tetrahydrofuran, 1,4-dioxane, t-butyl methyl ether, ethyl  
 acetate, methyl acetate, propyl acetate, isopropyl acetate,  
 15 butyl acetate, isobutyl acetate, pentyl acetate, methyl  
 propionate, ethyl propionate or a mixed solvent thereof.

40. The crystallization method according to Claim 37  
 wherein the good solvent is dichloromethane,  
 20 1,1-dichloroethane, 1,2-dichloroethane,  
 1,1,1-trichloroethane, 1,1,2-trichloroethane or a mixed  
 solvent thereof.

41. The crystallization method according to Claim 40  
 25 wherein the good solvent is dichloromethane.

42. The crystallization method according to any one of  
 Claims 28 to 41  
 wherein the addition of the aliphatic hydrocarbon solvent  
 30 to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-  
 L-alanine N-carboxylic anhydride in the good solvent is carried  
 out under stirring with a stirring force corresponding to a  
 stirring power requirement of not less than 0.1 kW/m<sup>3</sup>.

35 43. The crystallization method according to Claim 42



wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is carried out under stirring with the stirring force corresponding to the stirring power requirement of not less than  $0.3 \text{ kW/m}^3$ .

44. The crystallization method according to any one of Claims 28 to 43

wherein the addition of the aliphatic hydrocarbon solvent to the solution of N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine N-carboxylic anhydride in the good solvent is carried out by preparing a slurry of said N-carboxylic anhydride in advance and adding the aliphatic hydrocarbon solvent sequentially to said slurry.

15

45. The crystallization method according to Claim 44 wherein a suspension amount of the slurry of said N-carboxylic anhydride to be prepared in advance is not more than 30 weight % based on the total amount of said N-carboxylic anhydride at completion of the crystallization.

20

46. The crystallization method according to Claim 44 or 45

wherein the preparation of the slurry is carried out by sequential addition of the aliphatic hydrocarbon solvent to the solution of said N-carboxylic anhydride in the good solvent and/or by addition of a crystal of said N-carboxylic anhydride to the solution of said N-carboxylic anhydride in the good solvent.

30

47. The crystallization method according to Claim 46 wherein the aliphatic hydrocarbon solvent is added to the solution in the good solvent in such a proportion that a weight ratio of the good solvent to the aliphatic hydrocarbon solvent is 0.1 to 10 at a preliminary crystallization.

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48. The crystallization method according to any one of Claims 28 to 47

5 wherein the weight ratio of the good solvent to the aliphatic hydrocarbon solvent is 0.001 to 1 at completion of the addition.

49. The crystallization method according to Claim 48 wherein the weight ratio of the good solvent to the  
10 aliphatic hydrocarbon solvent is 0.003 to 0.8 at completion of the addition.

50. The crystallization method according to any one of Claims 28 to 49  
15 wherein an amount of a precipitated crystal is increased by adjusting a liquid temperature to -30 to 25°C following completion of the addition.

51. The crystallization method according to any one of  
20 Claims 28 to 50

wherein the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine  
N-carboxylic anhydride in the good solvent is  
an NCA forming reaction solution obtained by reacting  
25 N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine with  
N,N'-carbonyldiimidazole or phosgene or  
a solution obtained by subjecting the reaction solution  
to concentration or solvent exchange.

30 52. The crystallization method according to Claim 51 wherein an impurity or a coloring component as a byproduct of the NCA forming reaction is removed by using an adsorbent prior to the crystallization.

35 53. The crystallization method according to Claim 51 or

wherein an NCA forming reaction solvent doubles as the good solvent for the solution of  
N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanine

- 5 N-carboxylic anhydride in the good solvent.